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Models for *Trypanosoma evansi* (surra), its control and economic impact on small-hold livestock owners in the Philippines

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Abstract

Simple demographic and infectious disease models of buffalo and other domestic hosts for animal trypanosomosis (surra) caused by *Trypanosoma evansi* were developed. The animal models contained deterministic and stochastic elements and were linked to simulate the benefit of control regimes for surra in village domestic animal populations in Mindanao, Philippines. The impact of the disease on host fertility and mortality were key factors in determining the economic losses and net-benefit from the control regimes. If using a high (99%) efficacy drug in surra-moderate to high risk areas, then treating all animals twice each year yielded low prevalence in 2 years; targeted treatment of clinically sick animals, constantly monitored (monthly), required 75% fewer treatments but took longer to reach a low prevalence than treating all animals twice each year. At high drug efficacy both of these treatment strategies increased the benefit over untreated animals by 81%. If drug efficacy declined then the benefit obtained from twice yearly treatment of all animals declined rapidly compared with regular monitoring and targeting treatment to clinically sick animals. The current control regimen applied in the Philippines of annual sero-testing for surra and only treating sero-positive animals provided the lowest net-benefit of all the control options simulated and would not be regarded as effective control. The total net-benefit from effective surra control for a typical village in a moderate/high risk area was 7.9 million pesos per annum (US $158,000). The value added to buffaloes, cattle, horses, goats/sheep and pigs as a result of this control was US $88, $84, $151, $7, $114 per animal/year, respectively.

Keywords: Trypanosoma evansi; Cost benefit; Control strategies; Targeted treatment; Infectious disease model; Philippines

1. Introduction

The epidemiology of *Trypanosoma evansi* (surra) results from interactions between the main tabanid arthropod-vectors (*Tabanus* spp.), climate, susceptibility of hosts, animal stress and movement, pathogenicity of the parasite, and the structure of domestic and wild animal populations (Luckins, 1998; Reid, 2002). In the high surra-risk areas in Mindanao, tabanids are abundant throughout the year (unpublished data) facilitating transmission of *T. evansi* amongst susceptible village buffalo and other host animals that are usually tethered together in common pasture areas. Stress due to farm work and concurrent diseases assists the survival of the parasite in animal hosts, while constant movement of animals within the island due to trade, a government dispersal programme and transmigration of people favours the spread of the disease. Surra is considered one of the most economically important animal parasitic diseases in the Philippines (Manuel, 1998), particularly in Mindanao. While buffaloes and cattle are believed to be the main reservoir hosts for *T. evansi* harbouring chronic disease, mortality and morbidity may also occur in these animals. Horses are most susceptible to surra, showing acute disease and high mortalities (Silva et al., 1995), while goats and pigs are also likely to be infected (Manuel, 1998; Reid, 2002; Dargantes et al., 2005: Holland et al., 2003). Reduced fertility and mortality were observed in buffalo populations in surra-high risk areas (Dargantes et al., 2009). However, despite the impact of surra on animal productivity, financial losses due to the disease are potentially underestimated due to insufficient data, misdiagnosis, remoteness of the affected areas, and reluctance of the farmers to report mortalities.

Surra can only be effectively controlled through the use of curative drugs, which are relatively expensive and not widely available. Of the drugs available only melarsomine hydrochloride (Cymelarsan^{R}) and diminazine aceturate (Berenil^{R}, Surraplex^{R}, Trypan^{R}) are considered safe for use in all animal species. Nevertheless, melarsomine is the only drug that has demonstrated satisfactory efficacy in south-east Asia (Lun et al., 1991; Payne et al., 1994) but it is not currently marketed in the Philippines. In recent years, the Philippine government has implemented an extensive Mindanao-wide control programme known as the Mindanao Unified Surra Control Approach (MUSCA). It was designed to reduce the incidence of surra in endemic areas to avoid further economic losses and to prevent its spread to other provinces. The programme which mainly involved chemotherapy using diminazene, also included educating farmers on the life cycle and health impact of surra, capability-building of technicians and regional laboratories for better disease

diagnosis, supportive treatment and disease monitoring. The endeavour has been successful in reducing damage due to the disease (R.T. Mercado, personal communication); however, sporadic epidemics have occurred in recent months. There is therefore a need to assess the economic benefits of the present chemotherapy regimen and other practical treatment options in order to justify the continuation of a more cost-effective, sustainable control strategy against the disease. In this study, a disease model for surra in village buffalo and other animal hosts was developed to simulate losses due to the disease and evaluate financial benefits of six treatment regimens. Data from a cross-sectional survey of the seroprevalence of *T. evansi* conducted in Mindanao (Dargantes et al., 2009) was used to estimate parameters for the host population demographic and infectious disease models. Treatment costs and the benefits gained by animals achieving their full reproductive potential were included in the model as a measure of the productivity from village/small-hold farms in the Philippines. Rate parameters associated with birth, death, disease transmission and chemotherapy were treated as random variables for the purpose of Monte Carlo simulation. Cost parameters were fixed in the model as the effect of the disease on productivity was the primary concern of the study rather than accounting for the impact of fluctuations in market price. Changes in vector populations, normally subject to climate temperature and moisture variables, were modelled in a simplistic way by assuming tabanid abundance changed smoothly between preset peak season abundance and minimum levels which occurred 6 months after the peak. Having developed this model for a well-defined endemic region it can be applied to other areas where surra poses a risk or it can be used to predict the likely dynamics of disease if surra were introduced to a surra-free zone.

2. Materials and methods

2.1. Surra/buffalo infectious disease (SIC) model

For hosts, three disease states were modelled, Susceptible-infectious-subclinical (SIC) - transition between these states was dependent on vector capacity, prevalence, host resilience and chemotherapy as set out below. Data from a 4-year (2002-6) survey of village buffaloes and other animal hosts from five provinces in Mindanao, Philippines were used to define the model framework (Dargantes et al., 2009).

Additional initial data from an on-going 2007-8 Mindanao survey of buffaloes, pigs and goats were also utilised to estimate the relevance of the host species in the disease epidemiology.

2.1.1. Transition states

Tables 1-2 and Fig. 1 show the details of the transitions in the SIC model for buffaloes. Note there is no transition from the two infected states (infectious (i) and subclinical (c)) to the uninfected-susceptible state, which is a common transition for some bacterial and viral diseases (i.e. susceptible-infectious-resistant-susceptible (SIRS) models). However, the simulation model allows for drug treatment and in this case the number of infected animals successfully treated in a time-step are moved to the appropriate uninfected cohorts (So or Ro, the uninfected innate susceptible and resistant hosts, respectively). Also, animals cannot go directly to a subclinical cohort without first becoming infectious (clinically infected). The simulation model time-step was 1 month and the framework described here for buffalo was used for other hosts by changing the relevant production and infection parameters (Table 3).

2.1.2. Vector transmission

Trypanosoma evansi is mechanically transmitted between buffalo and other host species by tabanid flies. Infection success is dependent on the fly intensity, host susceptibility, disease prevalence and level of parasitaemia in infected animals (Desquesnes et al., 2009). Tabanid intensity or attack rate (arbitrarily set with potential range 0 to10) was assumed to be seasonal and defined by a cosine-curve (Fig. 2) with three parameters: *maxMonth*, *max* and *min* which fix the month of maximum fly intensity and the maximum and minimum levels, respectively. The minimum level intensity was assumed to occur 6 months after the maximum level, with *Vector Intensity* (`Vi`) defined by the cosine-curve as:

`Vi` = *min*+[(*max*-*min*)*{1+cos(*angle*)}/2], where *angle* is the *month* transformed to an angle by:

angle = (*month*-*maxMonth*)*360/12 and *month* was 1, 2, 3… for Jan, Feb, March etc., note angle is converted to radians before use in the cosine function. The parameters `StoI` and `RtoI` are the probability that infection will result from a bite from a fly carrying the parasite for the innate susceptible and resistant cohorts, respectively. The transition from susceptible to infectious as determined by the equations shown in Tables 1 and 2 is similar to the "frequency-dependent transmission" defined by Begon et al. (2002). However here, `I/N` represents the proportion of infectious animals, not prevalence, because it was assumed

that a proportion of subclinical animals do not have high enough parasitaemia to allow biting tabanids to acquire any trypanosomes. The proportion of subclinical animals that contribute to the total pool of infectious animals was determined from the parameter `SCinfect` (Table 2). To estimate transmission success the proportion of infectious animals (`I/N`) was further amplified or decreased by `Vi` to yield `V` (i.e. `V=Vi*I/N`), which was used in the model as shown in Table 1. It is not unreasonable for `V` to exceed one as this would indicate multiple contacts with flies carrying infection. However, if `V*StoI` or `V*RtoI` exceed one, which is possible at high prevalence and high vector intensities, then this product is reset to one as only 100% of uninfected hosts can be converted to infectious. `Vi` is a parameter that combines a number of parameters associated with the vector such as: fly-host contact rate, the probability that a fly acquires a trypanosome(s) from an infected animal, the probability of successfully transferring a viable trypanosomes to an uninfected host (vector competence) and fly intensity. Measurement of all such parameters are currently not available so the above seasonally defined `Vi` between set levels substitutes for a more comprehensive exploration of vector competence. The parameter `minN` was included to represent a pool of uninfected non-buffalo hosts (in buffalo equivalents) that are also tabanid targets but generally maintain a lower surra-seroprevalence than buffaloes (e.g. goats, dogs, pigs etc.). For large buffalo populations or simulations that included these hosts this factor is not applied, as was the case for this study. However, for small populations `N` is increased to the minimum value if necessary.

2.1.3. Summary

An arbitrary scale of 0 to 10 was chosen to represent vector intensity (`Vi`). Seasonal fluctuations between the maximum and minimum levels of `Vi` (set by the user) was defined by a cosine-curve, this curve provides the fly intensity for a particular month. The `Vi` value was then reduced by the current proportion of infectious animals (`I/N`) to give `V` (the monthly transmission coefficient). However, if `N` was less than `minN` then the proportion infectious was set to `I/minN`. That is, `V = Vi*I/minN` becomes the monthly transmission coefficient for small herds. Finally, the proportion of uninfected animals that became infected in a particular month was `V*StoI` and `V*RtoI` for the innate susceptible and resistant hosts, respectively.

2.1.4. Drug treatment, animal harvest and import

The efficacy of the drug, the proportion of each cohort treated and frequency of treatment were control/user-defined management parameters (see Table 2). The proportion of animals successfully treated (e.g. `Efficacy*TreatI`) in a particular time step was removed from the infected groups and returned to the uninfected groups; no immunity was assumed to be conferred by prior infection (Donelson et al., 1998). If the number of drug treatments/year were set at 0.5, 1 or 2… then a simulation treatment would be scheduled once in 24, 12 or 6… months etc. Annual birth and death rates were converted to monthly rates, at each time step the number of dead animals was removed from each cohort, and then excess males (or females, depending on the set sex ratio) were removed (harvested), as calves, to maintain the initial sex ratio. If the resulting population exceeded the initial population then additional animals were harvested, or if necessary animals were imported to maintain the original herd size. Any animals imported were assumed to be uninfected. The model was developed in Excel (Microsoft Inc., USA).

2.1.5. Cattle, horse, sheep/goat and pig hosts

The SIC model described above was also used to simulate infections in non-buffalo hosts by changing the relevant parameters (see Table 3). Separate Excel workbooks for each host species were opened simultaneously to exchange information on host numbers and vector intensity. A Relative Host-Vector Ratio was defined to convert different host to buffalo equivalents for the purpose of estimating vector transmission and the ratio of infectious to uninfected animals for all host species at risk in an area; this is similar to that described by Doran et al. (2005) for viral disease in feral pigs. This ratio was defined as the number of non-buffalo animals that attracted the same number of flies that were on one buffalo, (e.g. if a buffalo had attracted 60 flies while a cow attracted 30 flies then two cows was equivalent to one buffalo and the cow ratio would be set at 2). The proportion of infectious animals (`I/N`) was determined by converting all hosts to buffalo equivalents using the relative ratios shown in Table 3, the composite estimate of `I/N` was used as described above. The relative ratios were also used to scale the attack rate per host species, e.g. if the vector intensity (`Vi`) was 5 (for buffalo) then it was scaled to 2.5 and 0.5 for cattle and goats respectively using the ratios from Table 3. However, `I/N` remained common for all species. Like `Vi,` the Relative Host-Vector Ratio simplifies a number of complex issues into a single parameter, e.g. host size, tabanid host-specificity, hosts defensive activities and animal management practices. The latter is likely to play a major role in determining the exposure of animals to tabanids. Manresa et al. (1935) found oxen on open pasture

attracted 18 times more tabanids than oxen under shelter. The estimates used here are based on anecdotal observations by veterinarians visiting surra outbreaks in Mindanao (expert opinion) and take into account the local management of the different host species.

2.2. Evaluation of control regimens with the SIC model

The SIC model was used to estimate the success of different treatment regimens in a typical village of moderate/high surra risk and included buffaloes, goats/sheep, pigs, horses and cattle as these are the animals of major economic or production importance. Simulations were run for 15 years, however, results focused on the first 5 years after intervention. Six drug treatment regimens were simulated: (1) twice yearly treatment of all animals; (2) twice yearly treatment of horse, cattle and buffalo (goat and pigs remained untreated); (3) targeted treatment of all animals showing clinical signs, monitored monthly; (4) targeted treatment of horses, cattle and buffaloes showing clinical signs (goats and pigs remained untreated), monitored monthly; (5) annual diagnostic testing of buffaloes, cattle and horses, and only treating sero-positive animals; (6) no treatment of any hosts. Regimens 1-4 were considered realistic practical options for Mindanao. Regimen 5 is currently applied in Mindanao but in practice additional treatments are also applied in response to a disease outbreak. For regimens 1-5 drug efficacy was assumed to be 99% (i.e. for melarsomine); regimen 5 was also simulated with the efficacy set to 80% (regimen 5a) to represent diminazene aceturate use.

To simulate these regimens, additional assumptions were made. When estimating the total number of drug treatments required for regimens 1-5, drug treatment was stopped for a host species when no new clinical cases occurred in that species. For regimens 1-2 it was assumed that 100% of the host species targeted for treatment received treatment. The true cohort of clinically sick animals is shown in Table 1, however allowance was made for incorrect diagnosis at the time of treatment for regimens 3-4. Thus the drug treatment parameter values given in Table 3, for regimens 3-4, are the proportion of animals actually treated (when aiming to treat all clinically sick animals); these were set at 0.95, 0.2 and 0.03 for clinical, subclinical and uninfected animals, respectively. For regimen 5, the treatment of sero-positive animals is dependent on the sensitivity and specificity of the diagnostic test used; we set the proportion of clinical, subclinical and uninfected animals treated to 0.83, 0.83 and 0.04, respectively. This assumes 83%

sensitivity, 96% specificity (Reid and Copeman, 2003) based on the card agglutination test for *T. evansi* (CATT; Institute for Tropical Medicine, Antwerp, Belgium).

For Monte Carlo estimates of treatment outcomes, model parameters for proportion of animals treated, birth, death and transition rates were randomly varied for 500 simulations to estimate mean model results and their 95% confidence limits. Random selection for the parameters was from a pert distribution with the most likely value being that given in Table 3 or as described above. Random variables and Monte Carlo simulation were generated using PopTools (CSIRO, Australia) within Excel. The impact of drug resistance or using a low efficacy drug in regimens 1-4 was examined by setting drug efficacy to 100, 99, 95, 90, 80, 70…0% in additional simulations for these regimens.

2.3. Cost benefit analysis

The net-benefit for each drug regimen was obtained by subtracting the cost/benefit result for the untreated simulation (6) from the cost/benefit result for the drug treatment regimens (1 to 5), this was done to simplify the cost/benefit analysis by ignoring common costs and benefits. Because all species were maintained at a fixed level in the simulations, some common costs/benefits were assumed to be approximately equal. That is, let T, M and R represent animal Treatment, Maintenance and Replacement costs, respectively, and D, C and E represent benefits from animal Draft-power, Consumption and Export, respectively. If Bt and Bu are the benefits from treated and untreated regimens, respectively, then the net-benefit for a treatment regimen (Bt-Bu) is given by:

Bt-Bu = Dt-Du + Ct-Cu + Et-Eu - Tt -Mt+Mu -Rt+Ru this reduces to:

Bt-Bu = Et-Eu - Tt -Rt+Ru if we assume that under both regimens: (a) draft-power requirements are sufficient; (b) consumption of animals are similar; and (c) maintenance cost are similar. Thus the simplified cost/benefit analysis for each regimen needs only to account for T (drug purchase, application and test costs), R (purchase of replacement animals when needed) and E (sale of excess animals when available) if we only estimate the net-benefit for each treatment regimen. This represents a reasonable approximation, although healthy animals may have more draft capacity than untreated animals (i.e. Dt-Du$\geq$0); in contrast an increased turnover of pigs, for example, expected for effective treatment regimens, would possibly require increased feed inputs (i.e. -Mt+Mu$\leq$0) while increased animal consumption due to improved fertility providing excess animals is accounted for as an export benefit.

The average benefit/host (mean of the benefit of the five host types) in pesos was determined for each drug treatment regimen and the untreated hosts (i.e. $\{\sum Bi\}/5$ where Bi was the mean benefit/year for host type i and i=1…5). The total benefit for a regimen was estimated by:

Total benefit = $\sum Ni*Bi$ where Ni was the number of animals of host type i and i=1…5.

3. Results

3.1. Surra/buffalo SIC model

3.1.1. Buffalo, cattle, horse, sheep/goat and pig hosts

Table 4 shows long-term predicted prevalence in untreated animals for a range of vector intensities. Because buffalo were the primary survey target, relatively few non-buffalo hosts were sampled (see Table 2 in the accompanying paper by Dargantes et al. (2009)). Using the observed seroprevalence in buffaloes from Table 2 in the Dargantes et al., 2009 report as a reference point, a comparison between long-term modelled prevalence (Table 4) and observed seroprevalence for other host-species can be made. There was some reasonable agreement for cow, horse and pig prevalence. The observed seroprevalence in goats/sheep was moderate and low when the observed buffalo seroprevalence was high. However, the predicted prevalence in goats/sheep was relatively low for a broad range of buffalo seroprevalence. In Table 4, modelled horse prevalence is similar to cattle at low vector intensities but becomes higher than cattle at high vector intensity. This result was based on the need in the model for sustained import of horses to maintain the population in high vector intensity areas. If imports ceased, then horse populations rapidly died out, which is what has been observed in Mindanao in high risk areas (A.P. Dargantes personal communication).

3.2. Evaluation of control regimens with the SIC model

Table 5 gives the number of drug treatments required to prevent clinical disease (in the first 5 years) under each regimen for each host species (deterministic result using the most likely parameter value and stochastic results). The 95% confidence limits in Table 5 indicate that targeted treatment of clinically sick animals, monitored 12 times/year, required significantly fewer treatments than treating all animals twice per

year, i.e. regimens 3 and 4 had upper confidence limits less than 300 total treatments while regimens 1 and 2 had lower confidence limits greater than 500. Leaving pigs and sheep/goats untreated required approximately five-fold more buffaloes to be treated under the two treatments/year regimen (1 versus 2) and two-fold more under the targeted treatment regimen (3 versus 4) (see Table 5). For each host species and control regimen the predicted prevalence averaged over the first 5 years is given in Table 6. For regimen 5, prevalence was approximately halved (depending on host species) while regimens 1-4 generally reduced prevalence to less than 6%. The net-benefit from the five drug treatment regimens by comparison with untreated hosts are shown in Fig. 3. Because the net-benefit was derived by subtracting the benefit/cost of untreated animals (6) from each regimen (1 to 5) then in host or treatments with 95% net-benefit confidence limits that do not overlap with zero (x-axis) are significantly different from untreated animals (Fig. 3).

3.3. Cost benefit analysis

For a drug of 100% efficacy the mean benefit/host (averaged over benefit for host type) for regimens 1 to 6 was 11,527, 10,318, 11,527, 10,731, 8,960 and 6,355 pesos, respectively, i.e. the mean benefits for regimens 1 and 3 were both 81% larger than the benefit for untreated animals. The current practice of annual treatment of sero-positive buffaloes, cattle and horses only yielded a 40% improvement, even though the drug was assumed to provide 100% efficacy; in practice the efficacy is about 80%. Fig. 4 shows the increased mean benefit from untreated animals for regimens 1 to 4 at various drug efficacies. As drug efficacy declines the benefit for animals treated twice each year, regardless of disease status, declined steadily while little loss of benefit occurred for animals monitored monthly and treated if clinically sick (Fig. 4). At 50% efficacy the mean benefit/host was 8,935, 8,110, 11,182 and 10,370 pesos for regimens 1 to 4, respectively, i.e. about half the gain provided by treatments 1 and 2 was lost while less than 10% of the gain made by treatments 3 and 4 was lost due to reduced drug efficacy. The total benefit (sum of the benefit for all animals in a village) for untreated (6) and effective treated (1 or 3) regimens were 1.5 and 9.4 million pesos per annum, respectively. That is, the total net-benefit lost to a village by not applying effective surra control was 7.9 million pesos per annum or US $160,000/year (assuming 5,000 pesos is approximately US $100). In terms of the value added to the domestic livestock this was estimated to be US $88, $84, $151, $7, $114 per animal/year for buffaloes, cattle, horses, goats/sheep and pigs, respectively (deterministic result).

The means for the stochastic results are given in Fig. 3 in pesos; note the stochastic results tend to be slightly higher than the deterministic results.

4. Discussion

The advantage of using Excel to model an infectious disease is that irregular treatment regimens can be easily introduced to the simulation study by changing the column value associated with treatment. The ability to simultaneously model a number of host species, exposed to a common vector base, with an infectious disease model over a time-frame sufficient to forecast the demographic impacts on host populations has allowed the benefit of surra control on production to be assessed at the village or province level. The benefits estimated here are likely to be conservative because they do not account for reduced weight gain and milk yields associated with *T. evansi* infection, nevertheless there were substantial benefits from controlling surra in buffaloes, cattle and horses. The greatest variation in net-benefit was for pigs because small changes in fertility due to disease were amplified by the relatively large litter size and the short gestation. Horses also showed large variation because of their relatively high death rate when exposed to surra and their high replacement costs.

The model predicts that regular monitoring and targeted treatment of all clinically sick animals (including sheep/goats and pigs) was the best option, requiring few treatments to produce a low prevalence (Table 5-6). However, in practice this would require proper education of farmers as to the economic significance of surra and its symptoms, commitment by stock owners to detect and report the disease to authorities through an effective reporting system and the availability of drugs to be administered regularly if necessary. Treatment of all animals twice per year provides similar net-benefits to targeted treatment without the need for constant monitoring of animals at risk but this regime needs an initial high input cost sufficient to treat all animals and was dependent on using a drug with high efficacy (Fig. 4). Another disadvantage of this option is that systematic mass chemotherapy will increase the risk of selection for drug resistance (Uilenberg, 1998); drug resistance is a problem in trypanosomes in African and other Asian countries (El Rayah et al., 1999; Zhou et al., 2004) and may emerge in Mindanao under such a regimen. From Fig. 4 it is clear that if a drug of low efficacy is used or efficacy declines due to drug resistance, then

the best option is to regularly monitor and treat only clinically sick animals. Treating pigs and sheep/goats was important for disease control because leaving them untreated prolonged the period of new clinical cases in other hosts. However there was little financial benefit from the treatment of sheep/goats if considered in isolation from other hosts.

In conclusion, the model predicts that under the current surra control practice in the Philippines changing from a drug of low efficacy to one of high efficacy would only provide marginal benefits, if any, to farmers. However, treating all animals twice per year or regular monitoring and the targeted treatment of any clinically sick animals with a drug of high efficacy would provide a substantial benefit. Of these options, targeted treatment is recommended because there are reduced input costs, less labour, better trypanocidal activity in the face of declining efficacy and reduced risk of selection for drug resistance. This strategy would also be suitable in other countries where small-hold farmers routinely tether or house their stock overnight In this situation regular assessment of the animal's health would not impose additional animal-management demands on farmers.

This model is suitable for use in countries where surra is endemic (South-east Asia, India, Africa and Latin America) and can be applied at a village or regional scale. With minor modifications it could be applied to other mechanically-vector transmitted diseases similar to that suggested by Desquesnes et al. (2009). The model is currently being developed to include additional host species such as macropods and camels so it can be applied to Australian conditions where introduction of surra from south-east Asia is a potential bio-security threat. It will be used to explore various surra-outbreak scenarios to predict the likely disease prevalence in reservoir species, change in mortalities of susceptible species, host demographic changes and explore potential control/eradication options.

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Tables

Table 1

Simplified difference equations for resulting change (Δ) in cohort size in one time-step but not showing birth of calves and removal of dead and/or harvested animals from the cohorts.

Cohort	Change	=	Uninfected * proportion	- losses	+ gains
Uninfected	ΔSo	=	((1-Innate)*Yo)*(1-V*StoI)	- V*StoI*So	
Uninfected	ΔRo	=	(Innate*Yo)*(1-V*RtoI)	- V*RtoI*Ro	
Clinical	ΔSi	=	((1-Innate)*Yo+So)*(V*StoI)	- Si*ItoC	+ Sc*CtoI
Clinical	ΔRi	=	(Innate*Yo+Ro)*(V*RtoI)	- Ri*ItoC	+ Rc*CtoI
Sub-Clinical	ΔSc	=		- Sc*CtoI	+ Si*ItoC
Sub-Clinical	ΔRc	=		- Rc*CtoI	+ Ri*ItoC

Cohort size is represented by So,Ro,Si,Ri,Sc,Rc and Yo(calves), where S and R stand for innate susceptible and resistant adults, respectively. Parameter definitions are given in Table 2. After drug treatment the proportion of animals that are successfully cured are moved to the appropriate uninfected cohort (not shown in these equations).

Table 2

Parameters, definitions and symbols used in the buffalo susceptible-infectious-subclinical (SIC) model and Table 1. Rate parameters are given as annual rates. The range indicates the allowable input minimum and maximum limits for the parameters which are sufficiently wide to allow simulation of a variety of hosts.

Parameter	Value & range		Comment
Innate	0.1	0-1	Proportion with innate resistance
StoI	0.8	0-1	Infection success for uninfected innate susceptible
RtoI	0.2	0-1	Infection success for uninfected innate resistant
ItoC	1.0	0-1	Transition proportion from infectious to subclinical
CtoI	0.5	0-1	Transition proportion from subclinical to infectious
[a] Sex	0.7	0-1	Female proportion of the population
Birth Rates			
μro	0.475	0-40	Uninfected resistant-Ro female
μso	0.475	0-40	Uninfected normal-So female
μi	0.150	0-40	Infectious Si & Ri females
μc	0.150	0-40	Sub-clinical infected Sc & Rc females
Death Rates			
λy	0.115	0-1	Calf uninfected Yo
λro	0.115	0-1	Uninfected resistant Ro
λso	0.115	0-1	Uninfected normal So
λi	0.250	0-1	Infectious Si & Ri
λc	0.175	0-1	Sub-clinical infected Sc & Rc
Drug treatment			
TreatI	0.95	0-1	Proportion of Infectious animals treated
TreatC	0.20	0-1	Proportion of Sub-clinical animals treated
TreatY	0.03	0-1	Proportion of Uninfected animals treated
[a] Efficacy	0.99	0-1	Proportion of treated animals rendered uninfected

[a]	`Drug`	12	0-12	Number of drug treatments/year
Infection Dynamics				
[a]	`minN`	33	5-50	Minimum population for disease stability
[a]	`maxMonth`	5	1-12	Month in which the maximum fly intensity occurs
[a]	`Vi`	2 to 5	0-10	Arbitrary measure of Vector Intensity
`SCinfect`		0.2	0-1	Proportion of subclinical animals that are infectious
[a]	`V = Vi*I/N`			Vector transmission (for N >= minN)
[a]	`V = Vi*I/minN`			Vector transmission (for N < minN)
[a]	`N = So+Ro+Si+Ri+Sc+Rc+Yo`			Total buffalo population
[a]	`I = Si+Ri + SCinfect*(Sc+Rc)`			Number of infectious animals

[a] Indicates parameters/quantity were not subject to Monte Carlo simulation (stochastic) variation.

Note: all clinically sick animals were assumed to be infectious and a proportion of sub-clinical animals were infectious.

Table 3

The number of hosts per village, the relative attractiveness of host to vectors (the larger the number, the fewer tabanids/host), modified parameters to simulate disease in non-buffalo hosts and cost benefit analysis parameters.

Parameter or Value	Buffalo	Cattle	Horse	Sheep/Goat	Pig
[a] Number of hosts (Ni)	80	40	15	150	200
[a] Relative Host-Vector Ratio	1	2	1	10	12
Birth Rate	0.475	0.500	0.40	1.50	18
Infected Birth Rate	0.150	0.150	0.10	0.30	5
Death Rate	0.115	0.080	0.07	0.14	0.1
Clinical Death Rate	0.250	0.330	0.80	0.50	0.4
Subclinical Death Rate	0.175	0.175	0.80	0.50	0.4
Infection Rate Innate Susceptible Host	0.2	0.1	0.2	0.2	0.2
Infection Rate Innate Resistant Host	0.8	0.5	0.9	0.8	0.8
[a] *Cost/Benefit Parameters (Pesos)*					
Diagnostic cost per test	300	300	300	300	300
Drug costs per treatment	300	300	300	30	200
Labour cost per treatment	300	300	300	150	150
Sale or purchase price of replacement host	25000	25000	10000	1500	5000

[a] Indicates parameters/quantity were not subject to Monte Carlo simulation (stochastic) variation.

Table 4

The effect of increasing vector intensity on the long-term prevalence in untreated hosts. The fly intensity fluctuates between the given high and low value (see the cosine-curve in Fig. 2).

Fly	Model prevalence, long term in untreated hosts				
Intensity	Buffalo	Cow	Horse	Goat	Pig
0 to 2	41%	13%	12%	3%	2%
Set at 1.6	59%	25%	24%	6%	5%
2 to 5	74%	46%	47%	15%	14%
5 to 8	80%	59%	64%	27%	24%
8 to 10	81%	63%	71%	34%	31%

Table 5

The total number of drug treatments used in the first 5 years for regimens 1-5 and 5a. The deterministic result of the model is given under the column labelled 'Model'; the other columns give the mean (total number) and lower and upper 95% confidence limits (LCL, UCL) from 500 random simulations (Monte Carlo).

Host	Number of Drug Treatments				Number of Drug Treatments			
	Model	Mean	LCL	UCL	Model	Mean	LCL	UCL
	[a]**Regimen 1**				**Regimen 2**			
Buffalo	156	271	154	790	783	715	462	790
Cattle	78	79	77	80	77	198	77	397
Horse	28	33	26	59	86	100	25	150
Sheep/Goat	289	311	285	577	0	0	0	0
Pig	322	350	310	628	0	0	0	0
Total #	873	1044	852	2134	946	1013	564	1337
	Regimen 3				**Regimen 4**			
Buffalo	71	76	66	110	151	161	93	227
Cattle	27	27	26	29	27	28	26	41
Horse	4	5	1	8	5	6	2	13
Sheep/Goat	59	61	55	68	0	0	0	0
Pig	70	70	62	78	0	0	0	0
Total #	231	239	210	293	183	195	121	281
	Regimen 5				**Regimen 5a** (80% efficacy)			
Buffalo	157	166	81	252	189	188	106	258
Cattle	40	42	25	62	48	50	34	69
Horse	19	18	4	37	22	21	6	40
Sheep/Goat	0	0	0	0	0	0	0	0
Pig	0	0	0	0	0	0	0	0
Total #	216	226	110	351	259	258	146	367

[a]Regimens 1-5 assume a drug of 99% efficacy. Regimen 1: All animals treated twice/year. Regimen 2: Buffaloes, cattle and horses treated twice/year. Regimen 3: Targeted treatment of all clinically sick animals 12 times/year. Regimen 4: Targeted treatment of clinically sick buffaloes, cattle and horses 12 times/year. Regimen 5: Annually test and treat sero-positive buffaloes, cattle and horses. Regimen 5a: Annually test and treat sero-positive buffaloes, cattle and horses with an 80% efficacy drug.

Table 6.

The mean prevalence, for each regimen, over the first 5 years of treatment. Results are for the deterministic solution using the model parameters given in Table 3.

	Mean Prevalence Results for Years 1-5				
Regimen	Buffalo	Cattle	Horse	Sheep/Goat	Pig
Initial Starting Prevalence	70.0%	55.0%	60.0%	20.0%	15.0%
1) 2 Treatments/Year all hosts	4.4%	3.2%	3.4%	1.1%	0.9%
2) 2 Treatments/Yr. Buffalo, Cattle, Horse	5.8%	3.5%	4.9%	7.0%	6.6%
3) Targeted treatment of Clinical Animals	5.4%	4.1%	3.8%	1.4%	1.1%
4) Targeted Clinical Buffalo, Cattle, Horse	5.6%	4.1%	4.0%	6.7%	6.4%
5) Treatment of sero-positive animals	25.6%	10.5%	20.5%	10.9%	9.8%
5a) [a] Treatment of sero-positive animals	38.1%	16.7%	29.2%	13.0%	11.5%
6) No animals treated	74.9%	50.6%	49.9%	17.6%	15.2%

[a]A drug with 80% efficacy was used in regimen 5a; in regimens 1-5 the drug efficacy was set at 99%.

Note: Regimens 1-2 represent mass chemotherapy; Regimens 3-4 are targeted treatments requiring monthly monitoring; Regimens 5-5a are annual targeted treatments based on sero-testing.

Figures
Legends to Figures

Fig. 1. Susceptible-infectious-subclinical (SIC) Buffalo - *Trypanosoma evansi* Model. In the SIC model o, i and c indicate uninfected-susceptible, infectious (clinical infection) and subclinical-infected animals, respectively; lines pointing back to "Yo" indicate reproduction rate; lines cycling within a cohort indicate survival rate in that stage; lines connecting stages indicate survival and transition rate from stage to stage. Death rates for each stage are not shown. For simplicity this is not an age structured model. 'Innate Resistant' are a cohort of the population that are able to be infected but are more resistant to infection that the 'Innate Susceptible' cohort; if the innate-resistant-fraction (denoted Innate) is set to zero then the model simplifies to the lower four nodes in the diagram (i.e. Yo, So, Si and Sc). Note drug treatment, death and harvest rates of animals are included in the overall model but are not shown in the above simplified diagram or in Table 2 which sets out the equations for change at each time-step for this model.

Fig. 2. Observed tabanids caught on buffalo in open pasture (Manresa and Mondonedo, 1935), the raw data (Tabanids/host/hour ranges from 3 to 42) was scaled by dividing the observed values by 42 (shown as "●"). The line shows the cosine-curve when the three parameters values were: *maxMonth* = 4, *max* = 0.6 and *min* = 0.07. The curve was defined as: Scaled Tabanids/host/hour = *min*+[(*max*-*min*)*{1+cos(*angle*)}/2], where *angle* in radians is the month transformed to an angle by: *angle* = (month-*maxMonth*)*360/12 and month is 1, 2, 3… for Jan, Feb, March etc.

Fig. 3. Mean and 95% Monte Carlo Confidence Interval of the net-benefit for the five drug treatment regimens, using a drug with 99% efficacy. The net-benefit was obtained by subtracting the cost/benefit result for the untreated simulation (regimen 6) from the cost/benefit result for other regimens (1-5), thus hosts or regimens with 95% confidence limits that do not overlap with zero (x-axis) are significantly different from untreated animals. Regimen 5a is the same as regimen 5 but with a drug of 80% efficacy.

Fig. 4. The effect of declining drug efficacy on the benefit obtained for drug treatment regimens 1 to 4. The relative benefit is shown as the percentage improvement in mean benefit per host compared with untreated

animals (regimen 6). Regimens shown by × indicate only buffalo, cattle and horses were treated, ▲ indicates the treatment of all host species, the broken line (---) indicates two drug treatments per year and the solid line (——) shows regimens for the targeted treatment of clinically sick animals when monitored monthly.

Figure 1.

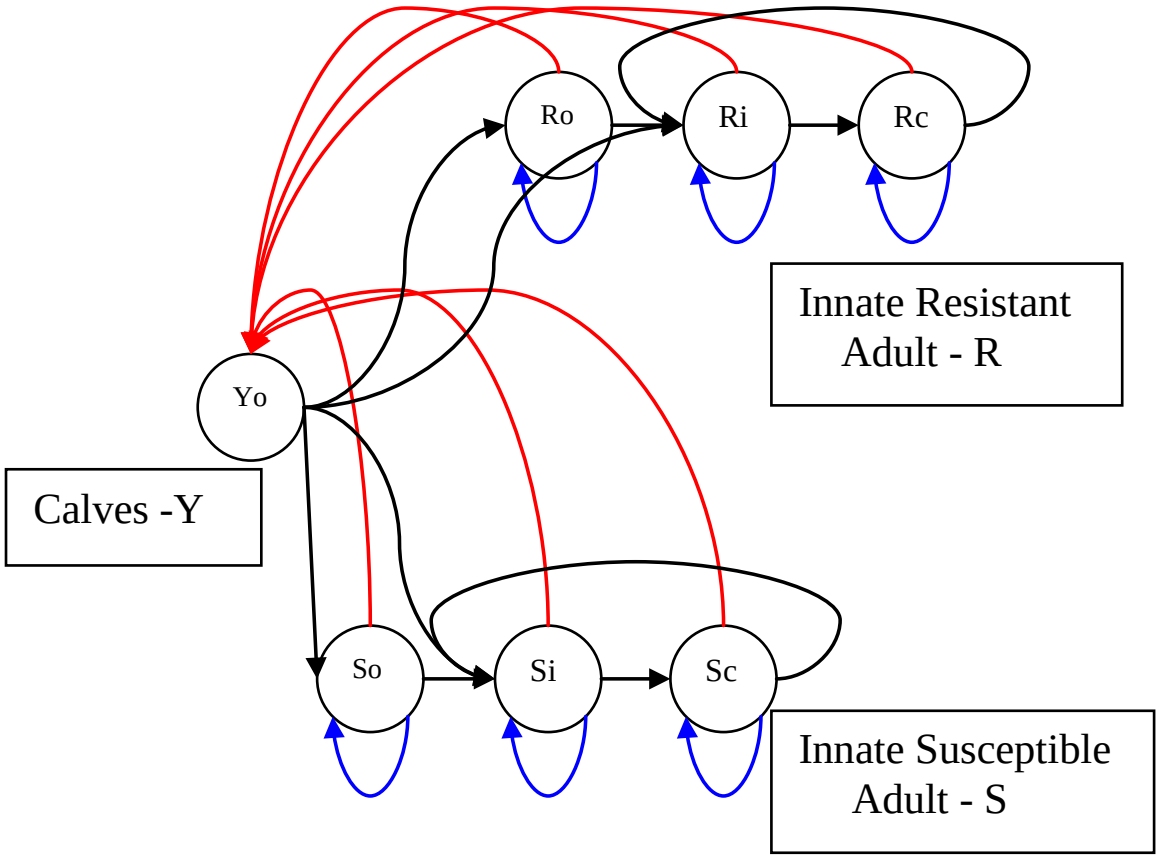

Ro
Ri
Rc
Innate Resistant Adult - R
Yo
Calves -Y
So
Si
Sc
Innate Susceptible Adult - S

Figure 2

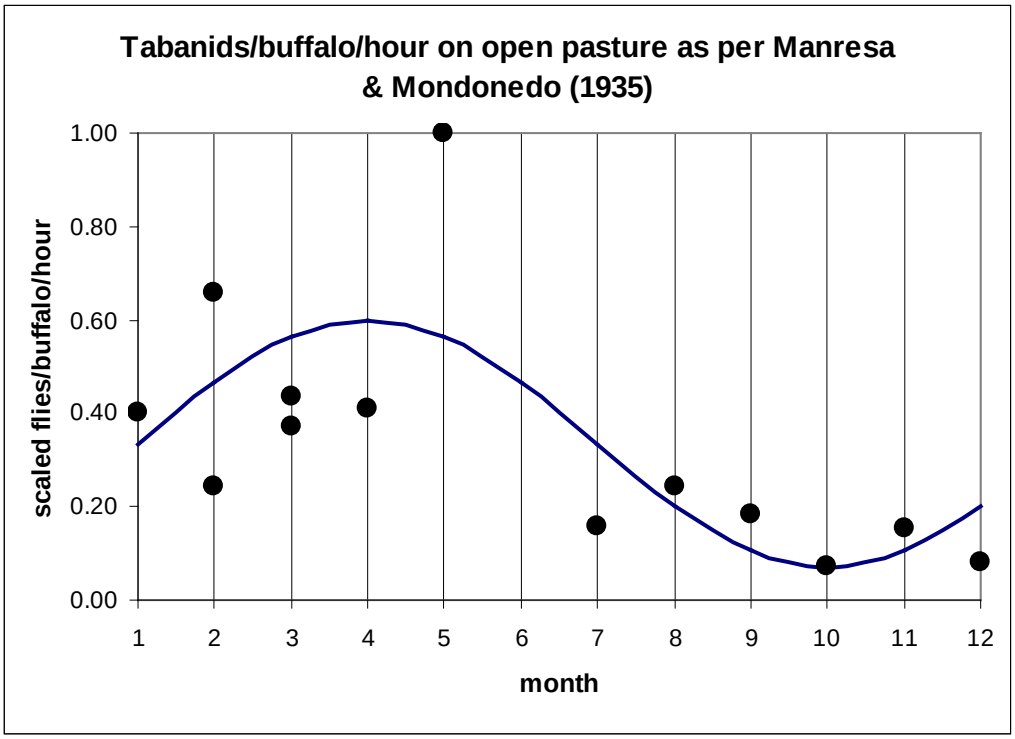

Tabanids/buffalo/hour on open pasture as per Manresa & Mondonedo (1935)
scaled flies/buffalo/hour
1.00
0.80
0.60
0.40
0.20
0.00
1
2
3
4
5
6
7
8
9
10
11
12
month

Figure 3

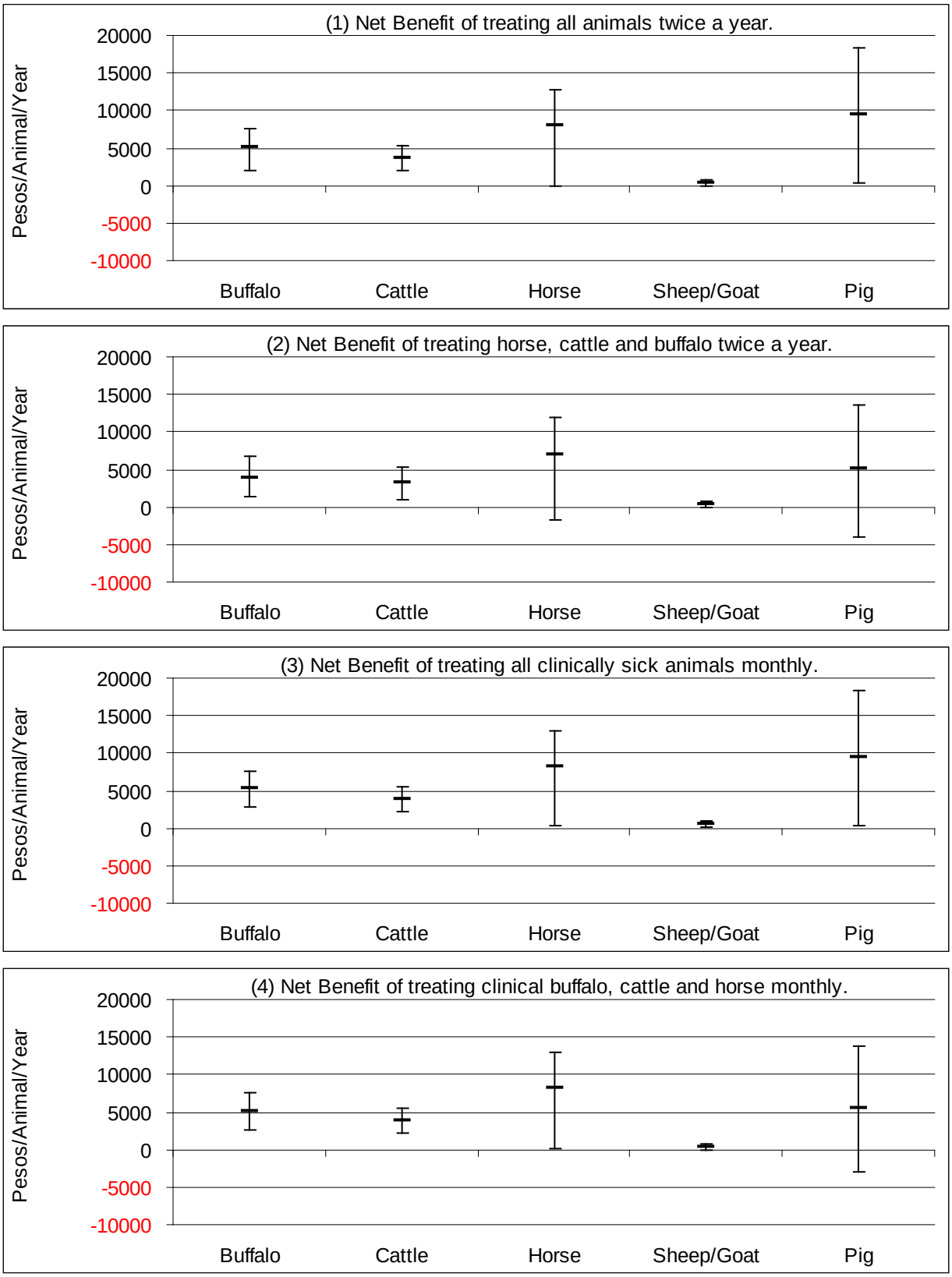
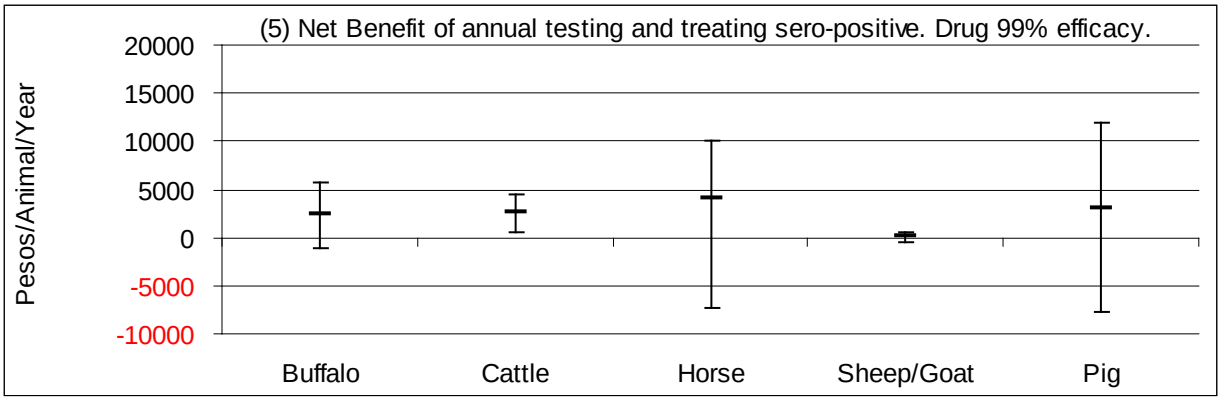


Figure 3 (continued over page)


(5) Net Benefit of annual testing and treating sero-positive. Drug 99% efficacy.
Pesos/Animal/Year
20000
15000
10000
5000
0
-5000
-10000
Buffalo
Cattle
Horse
Sheep/Goat
Pig

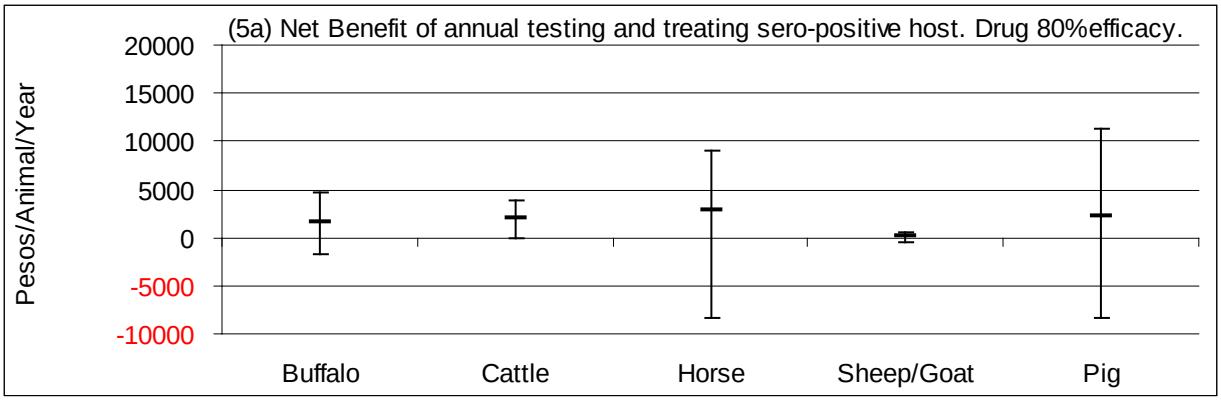
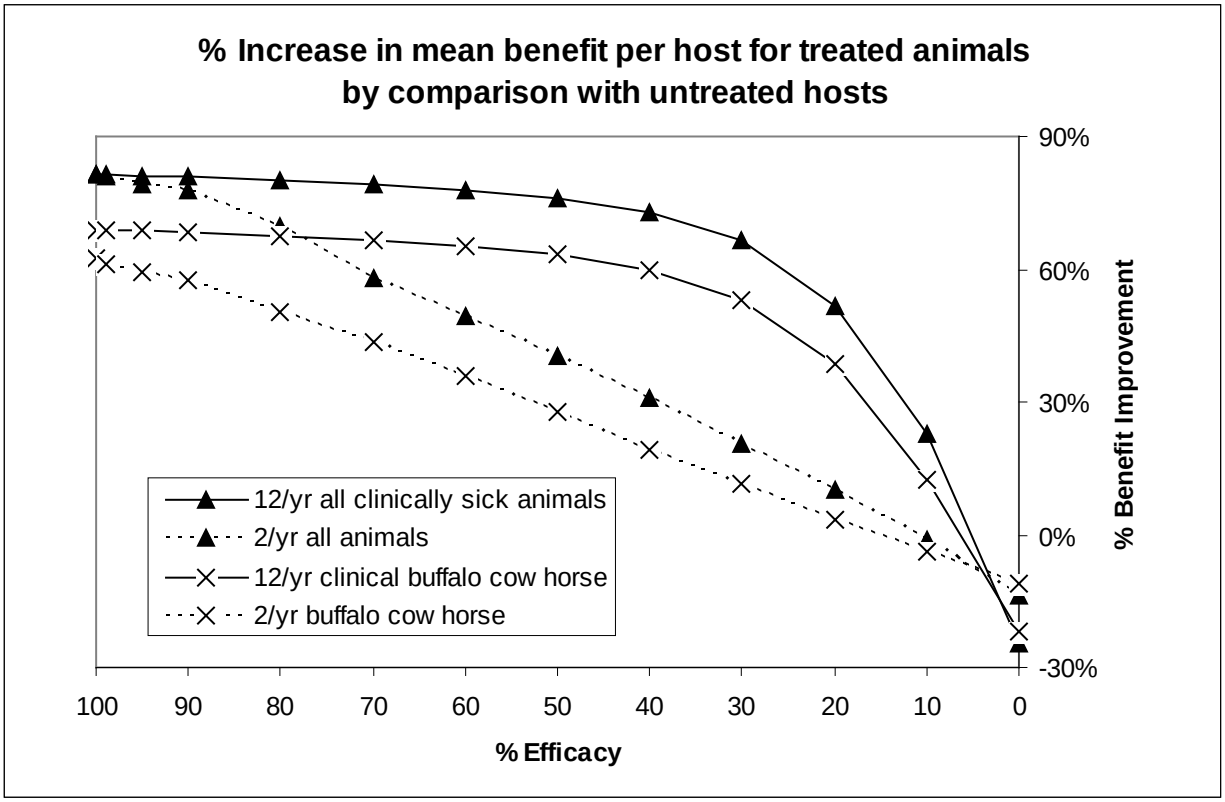

(5a) Net Benefit of annual testing and treating sero-positive host. Drug 80%efficacy.
Pesos/Animal/Year
20000
15000
10000
5000
0
-5000
-10000
Buffalo
Cattle
Horse
Sheep/Goat
Pig

Figure 4


% Increase in mean benefit per host for treated animals by comparison with untreated hosts
90%
60%
30%
0%
-30%
% Benefit Improvement
12/yr all clinically sick animals
2/yr all animals
12/yr clinical buffalo cow horse
2/yr buffalo cow horse
100
90
80
70
60
50
40
30
20
10
0
% Efficacy